Micellar Effects upon Dephosphorylation and Deacylation by Oximate Ions[1]

Clifford A. Bunton* and Yasuji Ihara[2]

Department of Chemistry, University of California, Santa Barbara, California, 93106

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Micelles of cetyltrimethylammonium bromide (CTABr) are very effective catalysts of the reactions of *p*-nitrophenyl diphenyl phosphate and *p*-nitrophenyl 3-phenylpropionate with *p*-nitrobenz-, 2-, 3-, and 4-pyridine- and 2-quinolinecarbaldoximate ion. The rate enhancements depend upon hydrophobicity of the nucleophile and for reactions of the phosphate range from 140-fold for 3-pyridinecarbaldoxime to 3700-fold for 2-quinolinecarbaldoxime, based on concentration of oximate ion. The rate constants measured using oxime in excess over substrate are approximately twice those measured under "burst" conditions using substrate in large excess over oxime. Although metal cations increase the nucleophilicity of the oximes, they do not assist reaction in the presence of CTABr.

Oximes are reactivators of phosphorylated acetylcholine esterase and related enzymes,[3] and their reactions with organic phosphates model this reactivation. It has also been found that the introduction of hydrophobic groups into the oxime can increase in vivo activity. They are also efficient deacylating agents, and the hydrolyses of their acyl and phosphoryl derivatives have been studied extensively.[4,5]

Our interest was in the effect of micelles upon these reactions,[6] because reactions at such submicroscopic interfaces should be better than reactions in homogeneous solution as models for the biological reactions. Reactions of benzaldoximes with *p*-nitrophenyl carboxylates are catalyzed by cationic micelles of cetyltrimethylammonium bromide (CTABr). There are many examples of deacylations by functional micelles or comicelles.[7-9,11] We have examined reactions of pyridine-, quinoline-, and *p*-nitrobenzaldoxime (I) with *p*-nitrophenyl diphenyl phosphate (II) because the pyridine aldoximes have been used as reactivators of choline esterase deactivated by various toxic phosphates.[3] We also examined the reactions with *p*-nitrophenyl 3-phenylpropionate (III) for purposes of comparison:

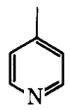
$$\underset{\text{I}}{\text{RCH=NOH}} + \underset{\text{II}}{(\text{PhO})_2\text{POC}_6\text{H}_4\text{NO}_2} \longrightarrow \text{RCH=NOPO(OPh)}_2 + \bar{\text{O}}\text{C}_6\text{H}_4\text{NO}_2$$

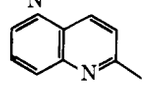
$$\text{RCH=NOH} + \underset{\text{III}}{\text{PhCH}_2\text{CH}_2\text{COOC}_6\text{H}_4\text{NO}_2} \longrightarrow \text{RCH=NOCO·CH}_2\text{CH}_2\text{Ph} + \bar{\text{O}}\text{C}_6\text{H}_4\text{NO}_2$$

Ia, R– = O_2N–C$_6$H$_4$–

b, R– = 

c, R– = 

d, R– = 

e, R– = 

Experimental Section

Materials. The substrates, surfactants, and the pyridinecarbaldoximes were prepared or purified by standard methods.[12,13] *p*-Nitrobenzaldoxime (Ia), prepared from aldelyde and hydroxylamine and recrystallized (aqueous EtOH), had mp 130–131 °C (lit.[5a] 130 °C). 2-Quinolinecarbaldoxime, similarly prepared,[14,15] had mp 185–186 °C (lit.[15] 184, 185–186, 188–190 °C). All the aldoximes have the syn configuration.[5,14-16] *N*-Decylglycine hydrochloride and N^{α}-decanoylhistidine were prepared by standard methods.[11a,17]

Dissociation Constants. The pK_as of the aldoximes were determined spectrophotometrically in water and CTABr (Table I), using the following wavelengths: Ia, 350 nm; Ib, d, 290 nm; Ic, 275 nm; Ie, 325 nm. Our pK_a values in water agreed reasonably well with other data. As expected, incorporation in the cationic micelle reduced pK_a, but the decrease was largest for the hydrophobic 2-quinolinecarbaldoxime (Ie), and for the pyridine aldoximes it was largest for the 2 isomer (Ib). These differences reflect the way in which the oxime fits into the micelle, and similar differences are found for micellar effects upon the strengths of carboxylic acids.[19] These pK_a values are apparent because they depend upon the pH at the micellar surface and the extent of oxime incorporations.

Kinetics. The formation of *p*-nitrophenoxide ion was followed spectrophotometrically at 410 (pH 8.0 and 10.0) and 350 nm (pH 6.0) and in most experiments the oxime concentration was much larger than that of the substrate ($0.75–1.5 \times 10^{-5}$ M). The buffers follow: pH 6.0, 0.02 M acetate; pH 8.0, 0.015 M borate; pH 10.0, 0.01 M borate. The pH of the reaction mixture was adjusted to these values. All reactions were at 25.0 °C.

Products

Hydrolysis of *O*-acylpyridine oxime gives oxime, with no dehydration to nitrile,[5b] and similar observations have been made on phosphorylated oximes.[4] We found no evidence of nitrile formation in the reaction of 10^{-4} M *p*-nitrobenz- or 2-quinolinealdoxime phosphate with 10^{-4} M *p*-nitrophenyl diphenyl phosphate in 5×10^{-3} M CTABr at pH 10. The products were examined by TLC (Eastman silica gel 13181 in 20% MeOH–$CHCl_3$).

Results and Discussion

Reaction of *p*-Nitrophenyl Diphenyl Phosphate with Oxime. Reaction in Absence of Surfactant. The second-order rate constants, k_2, are given in Table II, based on the concentration of oximate ion. The values at pH 10.0 are more reliable than those at pH 8.0 where only a small amount of the oxime is ionized to oximate and allowance has to be made for an appreciable contribution from reaction with water. All these oximate ions have very similar reactivities toward *p*-nitrophenyl diphenyl phosphate.

Reactions in CTABr. The reactions of the oximate ions with *p*-nitrophenyl diphenyl phosphate are very strongly catalyzed by cationic micelles (Figures 1 and 2). These rate constants are calculated using the concentrations of oximate ions and allowance is made for the reaction in the absence of oxime. The maximum rate enhancements (calculated in terms of concentrations of oximate ions) at pH 10.0 are in Table III, together with the concentration of CTABr for maximum rate enhancement.

The larger rate enhancements of the reactions of the *p*-nitrobenzaldoximate and 2-quinolinecarbaldoximate ion accord with the larger micellar effect upon the acid dissociations of the corresponding oximes as compared with those upon the

Table I. pK_a of the Oximes[a]

10^3[CTABr], M	Ia[b]	Ib[c]	Ic[d]	Id[e]	Ie[f]
	9.95 (9.91)	10.05	10.23	9.88	(9.79)
0.10	9.90 (9.90)	10.02		9.86	(9.74)
1.00	9.73 (9.59)	10.00	10.21	9.85	(8.88)
3.00	9.53 (9.34)				
5.00	9.47 (9.30)	9.88	10.18	9.82	(8.69)

[a] At 25.0 °C with 10^{-3} M oxime unless specified; values in parentheses are for 10^{-4} M oxime. Literature values: Ia, 10.36 in 12% EtOH;[5a] Ib, 10.4,[16a] 10.14,[18] Ic, 10.2,[18a] 10.36; [16b] Id, 10.2,[16a] 9.99.[16a] [b] Registry no., 1129-37-9. [c] Registry no., 873-69-8. [d] Registry no., 1193-92-6. [e] Registry no., 696-54-8. [f] Registry no., 1131-68-6.

Table II. Reactions with *p*-Nitrophenyl Diphenyl Phosphate in Water[a]

Oxime	k_2, M^{-1} s^{-1}
Ia	1.38 (1.00)
Ib	1.60 (1.26)
Ic	1.58 (1.31)
Id	1.16 (1.22)
Ie	1.87

[a] At 25.0 °C, with 10^{-4}–10^{-3}M oximate and pH 10.0. (The values in parentheses are at pH 8.0.)

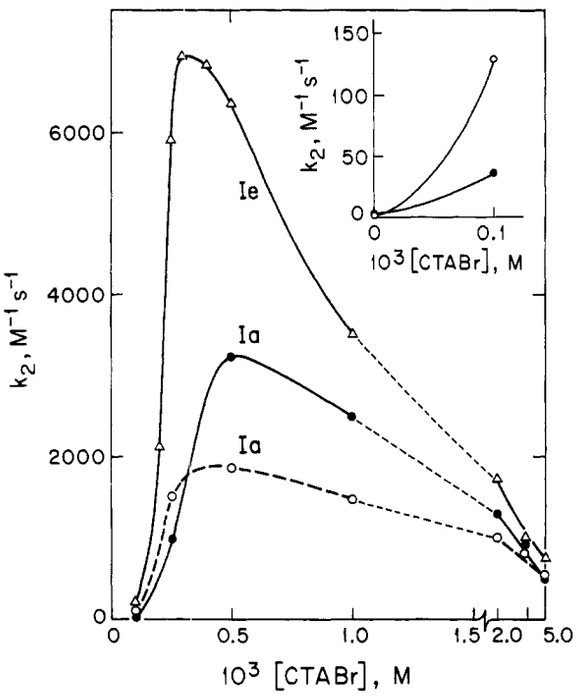


Figure 1. Reactions of *p*-nitrophenyl diphenyl phosphate with *p*-nitrobenz- and 2-quinolinealdoximate ions (Ia and Ie, respectively). Solid points at pH 10, open points at pH 8.0.

pyridine oximes (Table I), and the larger effect found with the 2-quinolinecarbaldoximate ion relative to the pyridine derivatives is typical of the beneficial effects of hydrophobicity upon micellar catalysis of nucleophilic attack.[7-9].

We include data for reaction at pH 8.0 in Figures 1 and 2 for purposes of comparison, and to illustrate the micellar catalysis at a pH close to that of physiological conditions. Comparison of micellar catalysis at the different pH is artificial, because we do not know the pH at the micellar surface,[20a] and the second-order rate constants at pH 8.0, based on our apparent pK_a values (Table I), are smaller than those at pH 10.0.

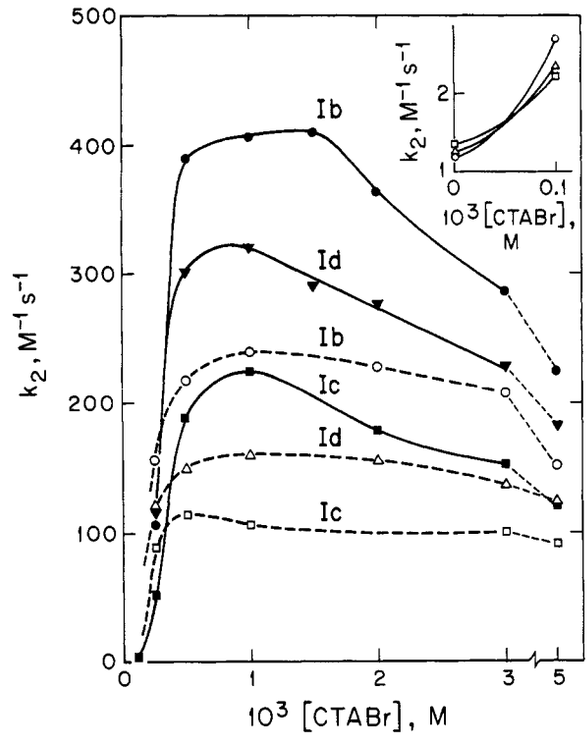


Figure 2. Reactions of *p*-nitrophenyl diphenyl phosphate with pyridinecarbaldoximate ions: 2-Ib; 3-Ic; 4-Id. Solid points at pH 10, open points at pH 8.0.

Table III. Micellar Catalysis of Reaction of *p*-Nitrophenyl Diphenyl Phosphate with Oximate Ions[a]

Nucleophile	k_2, M^{-1} s^{-1}	k_{rel}[b]	10^3[CTABr] max, M
p-Nitrobenzaldoximate	3230	2340	0.5
2-Pyridinecarbaldoximate	410	254	1.5
3-Pyridinecarbaldoximate	225	142	1.0
4-Pyridinecarbaldoximate	319	275	1.0
2-Quinolinecarbaldoximate	6940	3700	0.3

[a] At 25.0 °C, pH 10. [b] Calculated using rate constants at pH 10 in water and CTABr.

Table IV. Second-Order Rate Constants for Reaction of *p*-Nitrophenyl 3-Phenylpropionate[a]

	$10^{-2}k_2$, M^{-1} s^{-1}		
Nucleophile	H_2O	CTABr	k_{rel}
p-Nitrobenzaldoximate[b]	0.63	1380 (0.5)	2210
2-Pyridinecarbaldoximate[c]	0.78	239 (1.0)	307
3-Pyridinecarbaldoximate[c]	0.74	112 (1.0)	152
4-Pyridinecarbaldoximate[c]	0.55	155 (1.0)	283
2-Quinolinecarbaldoximate[d]	1.17	2230 (0.3)	1910

[a] At 25.0 °C; pH 8.0. The values in parentheses are the concentrations of CTABr (mM) for maximum catalysis. [b] 10^{-4} M. [c] 10^{-3} M. [d] 5×10^{-5} M.

Reaction of *p*-Nitrophenyl 3-Phenylpropionate with Oxime. Because of the fast deacylation at pH 10, we followed these reactions only at pH 8.0. The second-order rate constants for reactions with oximate ions are in Table IV, and the dependence on CTABr is shown in Figure 3 (allowance is made for reaction in the absence of oxime).

The rate constants for reaction of both the carboxylate and

Table V. Burst Kinetics[a]

Substrate	$10^5[S_0]$, M	Oxime $10^5[N_0]$, M	b, s^{-1}	$10^5\pi$, M	k_{II}, $M^{-1}\ s^{-1}$	10^3k_3, s^{-1}
III	12.0	Ie 2.5	0.31	2.67	2670	~0
III	12.0	Ie 5.0	0.32	4.97	2670	~2
II	10.0	Ie 2.5	0.0036	2.30	35	~0.2
II	10.0	Ie 5.0	0.0039	4.09	35	~0.4
II[b]	10.0	Ie 2.5	0.052	2.30	499	2.1
II[b]	10.0	Ie 5.0	0.043	4.62	417	1.6
II[b]	10.0	Ia 2.5	0.022	2.37	213	0.6
II[b]	10.0	Ia 5.0	0.019	4.15	178	1.6

[a] At 25.0 °C, 5×10^{-3} M CTABr and pH 8.0 unless specified. [b] pH 10.0.

Table VI. Secondary Release of *p*-Nitrophenoxide Ion[a]

Substrate	10^5 [substrate], M	Oxime	10^5 [oxime], M	10^3k_ψ, s^{-1}
III	1.5			1.6
III	12.0			2.2
III	12.0	Ie	2.5	3.4
III	12.0	Ie	5.0	3.7
II	1.5			0.066
II	10.0			0.057
II	10.0	Ia	2.5	0.078
II	10.0	Ia	5.0	0.077
II	10.0	Ie	2.5	0.062
II	10.0	Ie	5.0	0.063

[a] At 2.5 °C, pH 8.0 and 5×10^{-3} M CTABr.

phosphate ester increase sharply with increasing CTABr at low surfactant concentration when micelles begin to form (Figures 1–3, inserts); they rise to maxima and then decrease steadily. This behavior is common for bimolecular micellar catalyzed reactions and can be rationalized in terms of the partitioning of the two reagents between aqueous and micellar phases.[7-10,20]

In water there is little difference between the reactivities of the various oximate ions, and for reaction in CTABr the pattern is similar to that found with *p*-nitrophenyl diphenyl phosphate (Table III) except that the rate enhancements by CTABr are very similar for *p*-nitrobenzaldoximate and 2-quinolinecarbaldoximate ion.

"Burst" Experiments. In most of our experiments the aldoxime was in large excess over the substrate, but we also examined reaction in CTABr using excess substrate, so that there was a rapid evolution of *p*-nitrophenoxide ion followed by a slow reaction as the phosphorylated or acylated oxime was hydrolyzed to regenerate the nucleophile.

$$\mathrm{RCH{=}N\bar{O}} + \quad + (\mathrm{PhO})_2\mathrm{PO.OAr} \xrightarrow{k_{II}} \mathrm{RCH{=}NOH}$$

$$\mathrm{O\bar{A}r} + \mathrm{RCH{=}NOPO(OPh)_2} \xrightarrow[H_2O]{k_3} \mathrm{RCH{=}N\bar{O}}$$

A corresponding scheme can be written for deacylation, and k_{II} is calculated in terms of the total concentration of oxime.

The kinetic treatment is that of Bender and has been used by others.[22,23] If the initial concentrations of nucleophile and substrate are $[N_0]$ and $[S_0]$, respectively, π is the absorbance under steady-state conditions, extrapolated to time zero, t_0, and ΔA is the difference between the observed and extrapolated absorbances at time t, we obtain

$$\Delta A = \pi e^{-bt} \quad (1)$$

$$k_{II} = b\pi^{1/2}/[S_0][N_0]^{1/2} \quad (2)$$

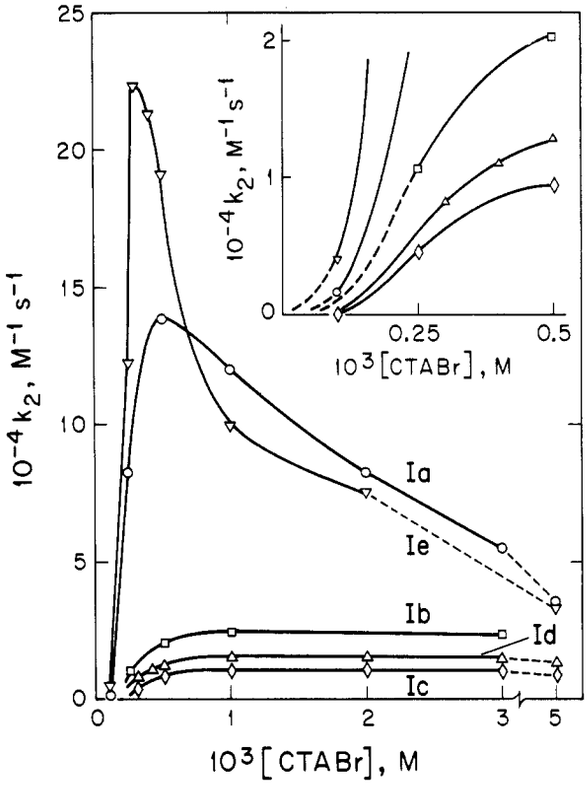


Figure 3. Reactions of *p*-nitrophenyl 3-phenylpropionate with oximate ions at pH 8.0.

Table VII. Second-Order Rate Constants Obtained under Different Conditions[a]

Substrate	Nucleophile	k_2, $M^{-1}\ s^{-1}$ "Burst"	k_2, $M^{-1}\ s^{-1}$ First order
II	Ia	320	510
II	Ie	480	760
III	Ie	16 000	34 600

[a] At 25.0 °C in 5×10^{-3} M CTABr; the reactions of the phosphate (II) were at pH 10.0 and those of the carboxylic ester (III) were at pH 8.0.

$$k_3 = b - k_{II}[S_0] \quad (3)$$

The values of b are obtained from the logarithmic form of eq 1 and give the parameters in Table V.

This treatment does not in our system give good values of k_3, which is calculated as the small difference between two larger numbers, so we also followed the secondary release of *p*-nitrophenoxide ion after establishment of steady-state conditions using substrate in excess over the oxime. Under these conditions some reactions are slow, and we then calcu-

Table VIII. Effect of Zinc (II) upon Deacylation[a]

		Nucleophile					
10^3[CTABr], M		Ib	Zn:Ib[c] 1:1	Zn:Ib[d] 1:2	Ie[b]	Zn:Ie[b,e] 1:1	Ia
	0.00095	0.0044	0.29		0.0046	0.0075	0.0034
0.25							0.90
0.50							38.4
1.00	0.034	5.59	3.11	3.83	37.6	36.9	58.3
2.00		5.67	3.19	3.47	31.9	28.8	53.3
3.00		6.01	3.29	3.53	21.7	20.5	43.3
5.00		4.60	2.75	3.40			34.0

[a] Values of 10^3k_ψ, s^{-1} at 25.0 °C, pH 6.0, 1.5×10^{-5} M substrate and added Zn(NO). The oxime concentration was 10^{-3} M unless specified. [b] 10^{-4} M. [c] Registry no., 35038-18-7. [d] Registry no., 15661-88-8. [e] Registry no., 62708-13-8.

Table IX. Effects of *N*-Decylglycine on Deacylation[a]

	Nucleophile	
10^4[$C_{10}H_{21}NHCH_2CO_2H$], M	Ib	Zn Ib
	5.59 (0.29)	3.11
2.5	5.23 (0.30)	4.63
5.0	6.23 (0.34)	5.50
7.0		5.80

[a] Values of 10^3k_ψ, s^{-1}, 10^{-3} CTABr, pH 6.0 and 1:1 zinc complex. The values in parentheses are in water.

Table X. Effect of Zinc(II) upon Dephosphorylation[a]

	10^4k_ψ, s^{-1}	
Nucleophile	H_2O	10^{-3} M CTABr
	0.020	1.48
10^{-3} M Ib		2.19
5×10^{-3} M Ib	0.028	
10^{-3} M Zn Ib		1.20
5×10^{-3} M Zn Ib	0.041	
10^{-4} M Ie		5.27
10^{-3} M Ia		6.39

[a] At 25.0 °C, pH 6.0.

lated the first-order rate constants by Guggenheim's method. These first-order rate constants (Table VI) are not much larger than those for the spontaneous hydrolysis in the absence of oxime, showing that the first formed oxime esters are hydrolyzed slowly, so that turnover of the oxime does not occur rapidly after the initial "burst" reaction.

One problem in following the initial burst of *p*-nitrophenoxide ion is that this has to be done, of necessity, using substrate in excess over the nucleophilic oxime,[24] whereas more usually the nucleophile is in large excess and reaction follows first-order kinetics. In Table VII, we compare the second-order rate constants, obtained from the "burst" kinetics and those with oximes in excess, calculated in terms of the total concentration of oximate ion. Consistently we obtain larger values of k_2 when we use oxime in excess, but the differences are not large, suggesting that at least for these reactions large changes in the reagent concentrations cause no major problems. The second-order rate constants in Table VII are lower than those given in Tables III and IV because the "burst" experiments were not carried out at the optimum surfactant concentration, but at a higher concentration where the reagents should be wholly in the micelles in order to minimize changes in micellar structure caused by high concentrations of the esters.

Effects of Structure of the Nucleophiles. Micellar catalysis of a bimolecular reaction requires that both reagents be incorporated into the micelles and the rate of the micellar catalyzed reaction depends upon the reactant concentrations and the second-order rate constant in the micelle. In water there are only small differences in the nucleophilicities of the oximate ions (Tables II and IV) suggesting that differences in k_{rel} (Tables III and IV) depend largely upon differences in micellar incorporation of the various oximate ions. This rationalization readily fits the results for the pyridine- and quinolinecarbaldoximes. It also suggests that the *p*-nitro group does not inhibit incorporation of *p*-nitrobenzaldoximate ion into the micelle, even though the hydrophilic groups (oximate- and nitro-) are at opposite ends of the ion so that if one is to be at the micellar surface the other would be expected to be in the micellar core. The micellar effects upon the apparent pK_a (Table I) are largest for *p*-nitrobenz- and 2-quinolinealdoxime as expected if these oximes are more effectively incorporated into the micelle than the pyridine aldoximes, so that both the rate and dissociation constants depend in similar ways upon the orientation of the oxime in the micelle.

It is customary to calculate micellar rate enhancements from the data at the rate maxima, but this approach is not particularly satisfactory because the rate–surfactant concentration profiles depend upon the distribution of both reagents between water and the micelles[10,20] so that we do not attach more than qualitative significance to the values of k_{rel} (Tables III and IV). However, these uncertainties appear to be most serious when one reagent is hydrophobic and the other hydrophilic, whereas in our system both nucleophile and substrate are relatively hydrophobic.

Reactions in the Presence of Zinc Ions. The zinc complex of 2-pyridinecarbaldoxime and other pyridine derivatives is a good nucleophile toward carboxylic esters,[18] and the role of zinc in activating carboxypeptidase has been reviewed.[25] However, metal chelates of 2-pyridinecarbaldoxime are not effective reactivators of phosphorylated acetylcholine esterase.[26] We have examined the effects of some zinc–aldoxime complexes in deacylation and dephosphorylation in the presence and absence of CTABr at pH 6.0. (The pK_a of these complexes is ca. 6.5.[18])

In agreement with existing evidence, these zinc complexes are effective reagents for the deacylation of *p*-nitrophenyl 3-phenylpropionate (III), but the rate enhancements by added CTABr were less than with the oxime alone (Table VIII), possibly because the cationic complex was not taken up readily by the micelle. The results with *p*-nitrobenzaldoxime (Ia) with no added zinc show that the pattern of the micellar catalysis is similar to those found at higher pH.

We also examined the effect of *N*-decylglycine on the deacylations (Table IX), because it seemed possible that additional chelation with the hydrophobic *N*-decylglycine might make it easier for the zinc complex to be taken up by the cationic micelle. The rate enhancements were small, and only slightly larger than those in the absence of zinc or CTABr, so

Table XI. Reaction of *p*-Nitrophenyl 3-Phenylpropionate in Comicelles of N^{α}-Decanoylhistidine

10^4[IV],[b] M	10^4[CTABr],[c] M	10^4[$Zn(NO_3)_2$],[d] M	10^3k_{ψ}, s^{-1}
1.0			0.14
1.0		1.0	0.15
1.0	1.0		1.71
1.0	1.0	1.0	2.70
5.0			0.27
5.0	50.0		11.2
5.0	50.0	5.0	9.48

[a] At 25.0 °C and pH 8.00. [b] Registry no., 55258-10-1. [c] Registry no., 57-09-0. [d] Registry no., 7779-88-6.

Table XII. Reactions in Comicelles of CTABr and N^{α}-Decanoylhistidine[a]

Substrate	Metal ion	10^3k_{ψ}, s^{-1}
II		0.58
II	0.5 mM $Zn(NO_3)_2$	0.64
II	0.5 mM $MgCl_2$	0.61
III		33.6[b]
III	0.1 mM $Zn(NO_3)_2$	46.0[b,c]
III	0.1 mM $MgCl_2$	39.3[b]
III	0.1 mM $Ca(NO_3)_2$	36.0[b]
III	0.1 mM Cd $(NO_3)_2$	31.9[b,c]
III	0.1 mM $CuSO_4$	54.3[b,c]
III	0.2 mM KCl	36.3[b]
III		33.1
III	0.5 mM $Zn(NO_3)_2$	36.6
III	0.5 mM $MgCl_2$	34.0

[a] At 25.0 °C and pH 8.0 with 5×10^{-3} M CTABr and decanoylhistidine unless specified. [b] 5×10^{-4} M CTABr and decanoylhistidine. [c] Precipitation occurred during reaction.

that any effects of *N*-decylglycine are relatively unimportant.

At pH 6.0 the reactions of *p*-nitrophenyl diphenyl phosphate are only slightly assisted by added aldoximes or their zinc complexes (Table X), which is reminiscent of the results with phosphorylated acetylcholineesterase.[26]

Reactions in the Presence of N^{α}-Decanoylhistidine (IV). Functional micelles or comicelles containing an imidazole moiety are effective deacylating and dephosphorylating agents. We carried out a few preliminary experiments (Tables XI and XII). When the surfactant concentrations were reduced so that precipitation did not occur we found only slight rate enhancement with added zinc nitrate, but in agreement with earlier evidence the catalytic effectiveness of hydrophobic histidine derivatives is strikingly increased by comicellization with CTABr.[11] We did not examine the kinetic effects of other metal ions systematically, but they appear to be small (Table XII).

Registry No.—II, 10359-36-1; III, 17895-71-5; *p*-nitrophenoxide ion, 14609-74-6; zinc, 7440-66-6; *N*-decylglycine, 20933-56-6.

References and Notes

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